

POLIVY[®]

Polatuzumab vedotin

1. NAME OF THE MEDICINAL PRODUCT

POLIVY 140 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 140 mg of polatuzumab vedotin.

After reconstitution, each mL contains 20 mg of polatuzumab vedotin.

Polatuzumab vedotin is an antibody-drug conjugate composed of the anti-mitotic agent monomethyl auristatin E (MMAE) covalently conjugated to a CD79b-directed monoclonal antibody (recombinant humanized immunoglobulin G1 [IgG1], produced in Chinese Hamster Ovary cells by recombinant DNA technology).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to greyish-white lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication(s)

Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.

4.2 Posology and method of administration

Polivy must only be administered under the supervision of a healthcare professional experienced in the diagnosis and treatment of cancer patients.

Posology

The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with bendamustine and rituximab for 6 cycles. Polivy, bendamustine and rituximab can be administered in any order on Day 1 of each cycle. When administered with Polivy, the recommended dose of bendamustine is 90 mg/m²/day on Day 1 and Day 2 of each cycle and the

recommended dose of rituximab is 375 mg/m² on Day 1 of each cycle. Due to limited clinical experience in patients treated with 1.8 mg/kg Polivy at a total dose >240 mg, it is recommended not to exceed the dose 240 mg/cycle.

If not already premedicated, premedication with an antihistamine and anti-pyretic should be administered to patients prior to Polivy.

Delayed or missed doses

If a planned dose of Polivy is missed, it should be administered as soon as possible and the schedule of administration should be adjusted to maintain a 21-day interval between doses.

Dose modifications

The infusion rate of Polivy should be slowed or interrupted if the patient develops an infusion-related reaction. Polivy should be discontinued immediately and permanently if the patient experiences a life-threatening reaction.

For dose modifications for peripheral neuropathy (section 4.4) see Table 1 below.

Table 1 Polivy dose modifications for peripheral neuropathy (PN)

Severity on Day 1 of any cycle	Dose modification
Grade 2-3	Withhold Polivy dosing until improvement to ≤ Grade 1. If recovered to Grade ≤1 on or before Day 14, restart Polivy at a permanently reduced dose of 1.4 mg/kg. If a prior dose reduction to 1.4 mg/kg has occurred, discontinue Polivy. If not recovered to Grade ≤1 on or before Day 14, discontinue Polivy.
Grade 4	Discontinue Polivy.

For dose modifications for myelosuppression see Table 2.

Table 2 Polivy, bendamustine and rituximab dose modifications for myelosuppression

Severity of myelosuppression on Day 1 of any cycle	Dose modification¹
Grade 3-4 Neutropenia	<p>Withhold all treatment until ANC recovers to >1000 μL.</p> <p>If ANC recovers to >1000 μL on or before Day 7, resume all treatment without any additional dose reductions.</p> <p>If ANC recovers to >1000 μL after Day 7:</p> <ul style="list-style-type: none"> restart all treatment, with a dose reduction of bendamustine from 90 mg/m² to 70 mg/m² or 70 mg/m² to 50 mg/m² if a bendamustine dose reduction to 50 mg/m² has already occurred, discontinue all treatment
Grade 3-4 Thrombocytopenia	<p>Withhold all treatment until platelets recover to >75,000 μL.</p> <p>If platelets recover to >75,000 μL on or before Day 7, resume all treatment without any dose reductions.</p> <p>If platelets recover to >75,000 μL after Day 7:</p> <ul style="list-style-type: none"> restart all treatment, with a dose reduction of bendamustine from 90 mg/m² to 70 mg/m² or 70 mg/m² to 50 mg/m² if a bendamustine dose reduction to 50 mg/m² has already occurred, discontinue all treatment

¹If primary cause is due to lymphoma, the dose of bendamustine may not need to be reduced.

For dose modifications for Infusion-related reactions see Table 3.

Table 3 Polivy, bendamustine, and rituximab dose modifications for Infusion-related reactions

Severity of IRR on Day 1 of any cycle	Dose modification
Grade 1-3 IRR	<p>Interrupt POLIVY infusion and give supportive treatment.</p> <p>For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue Polivy.</p> <p>For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Polivy.</p> <p>Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes.</p> <p>For the next cycle, infuse Polivy over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.</p>
Grade 4 IRR	<p>Stop Polivy infusion immediately.</p> <p>Give supportive treatment.</p> <p>Permanently discontinue Polivy.</p>

Special populations

Elderly

No dose adjustment of Polivy is required in patients ≥ 65 years of age (see section 5.2).

Renal Impairment

No dose adjustment of Polivy is required in patients with creatinine clearance (CrCL) ≥ 30 mL/min. A recommended dose has not been determined for patients with CrCL < 30 mL/min due to limited data.

Hepatic Impairment

The administration of Polivy in patients with moderate or severe hepatic impairment (bilirubin greater than $1.5 \times$ upper limit of normal [ULN]) should be avoided.

No adjustment in the starting dose is required when administering Polivy to patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to $1.5 \times$ ULN or aspartate transaminase [AST] greater than ULN).

Per studied population in mild hepatic impairment (defined as AST or ALT > 1.0 to $2.5 \times$ ULN or total bilirubin > 1.0 to $1.5 \times$ ULN), there was a 40% increase in unconjugated MMAE exposure, which was not deemed clinically significant.

Paediatric population

The safety and efficacy in children and adolescents (< 18 years) has not been established. No data are available.

Method of administration

Polivy is for intravenous use.

The initial dose of Polivy should be administered as a 90-minute intravenous infusion. Patients should be monitored for IRRs/hypersensitivity reactions during the infusion and for at least 90 minutes following completion of the initial dose.

If the prior infusion was well tolerated, the subsequent dose of Polivy may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion.

Polivy must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional. It should be administered as an intravenous infusion through a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 micrometer pore size) and catheter. Polivy must not be administered as intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Precaution to be taken before manipulating or administering the product

Polivy contains a cytotoxic component which is covalently attached to the monoclonal antibody. Follow applicable proper handling and disposal procedure (see section 6.6).

4.3 Contraindications

Polivy is contraindicated in patients with a known hypersensitivity to polatuzumab vedotin or any of the excipients.

4.4 Special Warnings and Precautions for useTraceability

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

Myelosuppression

Serious and severe neutropenia and febrile neutropenia have been reported in patients treated with Polivy as early as the first cycle of treatment. Prophylactic G-CSF administration was required in the clinical development and should be considered. Grade 3 or 4 thrombocytopenia or anemia can also occur with Polivy. Complete blood counts should be monitored prior to each dose of Polivy. More frequent lab monitoring and/or Polivy delays or discontinuation should be considered in patients with Grade 3 or Grade 4 neutropenia and thrombocytopenia (see 4.2 Dosage and Administration).

Peripheral Neuropathy (PN)

Peripheral neuropathy has been reported in patients treated with Polivy as early as the first cycle of treatment, and the risk increases with sequential doses. Patients with pre-existing peripheral neuropathy may experience worsening of this condition. Peripheral neuropathy reported with Polivy treatment is predominantly sensory peripheral neuropathy; however, motor and sensorimotor peripheral neuropathy have also been reported. Patients should be monitored for symptoms of peripheral neuropathy such as hypoesthesia, hyperesthesia, paresthesia, dysesthesia, neuropathic pain, burning sensation, muscle weakness, or gait disturbance. Patients experiencing new or worsening peripheral neuropathy may require a delay, dose reduction, or discontinuation of Polivy (see 4.2 Dosage and Administration).

Infections

Serious, life threatening, or fatal infections, including opportunistic infections, such as pneumonia (including *pneumocystis jirovecii* and other fungal pneumonia), bacteremia, sepsis, herpes infection, and cytomegalovirus infection have been reported in patients treated with Polivy (see 4.8 Undesirable Effects). Reactivation of latent infections has been reported. Patients should be closely monitored during treatment for signs of bacterial, fungal, or viral infections and seek medical advice if signs and symptom appear. Anti-infective prophylaxis should be considered throughout treatment with Polivy.

Polivy should not be administered in the presence of an active severe infection. Polivy and any concomitant chemotherapy should be discontinued in patients who develop serious infections.

Human Immunodeficiency Virus (HIV)

Polivy has not been evaluated in patients with HIV. With regard to co-administration of CYP3A-inhibitors see section 4.5.

Immunization

Live or live-attenuated vaccines should not be given concurrently with the treatment. Studies have not been conducted in patients who recently received live vaccines.

Progressive Multifocal Leukoencephalopathy (PML)

PML has been reported with Polivy treatment (see 4.8 Undesirable effects). Patients should be monitored closely for new or worsening neurological, cognitive, or behavioral changes suggestive of PML. Polivy and any concomitant chemotherapy should be withheld if PML is suspected and permanently discontinued if the diagnosis is confirmed.

Tumor Lysis Syndrome (TLS)

Patients with high tumor burden and rapidly proliferative tumor may be at increased risk of tumor lysis syndrome. Appropriate measures in accordance with local guidelines should be taken prior to treatment with Polivy. Patients should be monitored closely for tumor lysis syndrome during treatment with Polivy.

Infusion-related reactions

Polivy can cause IRRs, including severe cases. Delayed IRRs as late as 24 hours after receiving Polivy have occurred. An antihistamine and antipyretic should be administered prior to the administration of Polivy, and patients should be monitored closely throughout the infusion. If an IRR occurs, the infusion should be interrupted and appropriate medical management should be instituted (see section 4.2).

Embryo-Fetal Toxicity

Based on the mechanism of action and nonclinical studies, Polivy can be harmful to the fetus when administered to a pregnant woman. (see section 5.3). Pregnant woman should be advised regarding risk to the fetus.

Women of childbearing potential should be advised to use effective contraception during treatment with Polivy and for at least 9 months after the last dose (see section 4.6). Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose (see section 4.6).

Fertility

In non-clinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility (see section 5.3). Therefore, men being treated with Polivy are advised to have sperm samples preserved and stored before treatment(see section 4.6).

Elderly

Among 173 patients treated with Polivy in Study GO29365, 95 (55%) were ≥ 65 years of age. Patients aged ≥ 65 had a numerically higher incidence of serious adverse reactions (64%) than patients aged < 65 (53%). Clinical studies of Polivy did not include sufficient numbers of patients aged ≥ 65 to determine whether they respond differently from younger patients.

Hepatic Toxicity

Serious cases of hepatic toxicity that were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, have occurred in patients treated with Polivy (see section 4.8). Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Liver enzymes and bilirubin level should be monitored.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated clinical drug-drug interaction studies with Polivy in humans have been conducted.

Drug interactions with co-medications that are CYP3A inhibitors, inducers or substrates and co-medications that are P-gp inhibitors

Based on physiological-based pharmacokinetic (PBPK) model simulations of MMAE released from polatuzumab vedotin, strong CYP3A inhibitors and P-gp inhibitors (e.g., ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE by 48%. Caution is advised in case of concomitant treatment with CYP3A inhibitor. Patients receiving concomitant strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities.

Unconjugated MMAE is not predicted to alter the AUC of concomitant drugs that are CYP3A substrates (e.g., midazolam).

Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE.

Drug interactions of rituximab and bendamustine in combination with polatuzumab vedotin

The pharmacokinetics (PK) of rituximab and bendamustine are not affected by co-administration with Polivy. Concomitant rituximab is associated with increased antibody conjugated MMAE (acMMAE) plasma AUC by 24% and decreased unconjugated MMAE plasma AUC by 37%, based on population PK analysis. No dose adjustment is required.

Bendamustine does not affect acMMAE and unconjugated MMAE plasma AUC.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women

Women of childbearing potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 9 months after the last dose.

Men

Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with Polivy and for at least 6 months after the last dose.

Pregnancy

There are no data in pregnant women using Polivy. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the mechanism of action and nonclinical studies, polatuzumab vedotin can be harmful to the foetus when administered to a pregnant woman. In women of childbearing potential, the pregnancy status shall be checked prior to treatment. Polivy is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefit for the mother outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether polatuzumab vedotin or its metabolites are excreted in human breast milk. A risk for breast-feeding children cannot be excluded. Women should discontinue breast-feeding during treatment with Polivy.

Fertility

In nonclinical studies, polatuzumab vedotin has resulted in testicular toxicity, and may impair male reproductive function and fertility (see section 5.3).

Therefore, men being treated with this medicine are advised to have sperm samples preserved and stored before treatment. Men being treated with Polivy are advised not to father a child during treatment and for up to 6 months following the last dose.

4.7 Effects on ability to drive and use machine effects

Polivy has minor influence on the ability to drive and use machines.

Infusion related reactions, peripheral neuropathy, fatigue, and dizziness may occur during treatment with Polivy (see 4.4 Warnings and Precautions and 4.8 Undesirable Effects).

4.8 Undesirable Effects

4.8.1 Clinical Trials

Summary of the safety profile

For the clinical development program of Polivy as a whole, an estimated total of 588 patients have received Polivy. The adverse drug reactions (ADRs) described in this section were identified during treatment and follow-up of previously treated diffuse large B-cell lymphoma (DLBCL) patients from the pivotal clinical trial GO29365. This includes run-in phase patients (n=6) and randomized patients (n=39) who received Polivy in combination with bendamustine and rituximab (BR) compared to randomized patients (n=39) who received BR alone. Randomized patients in the Polivy treatment arm received a median of 5 cycles of treatment while randomized patients in the comparator arm received a median of 3 cycles of treatment.

The most frequently-reported ($\geq 30\%$) ADRs in patients treated with Polivy in combination with BR were anemia (46.7%), thrombocytopenia (46.7%), neutropenia (46.7%), fatigue (40.0%), diarrhea (37.8%), nausea (33.3%), and pyrexia (33.3%). Serious adverse events were reported in 27% of Polivy plus BR treated patients which included febrile neutropenia (6.7%), pyrexia (4.4%), and pneumonia (4.4%).

ADRs leading to treatment regimen discontinuation in $>5\%$ of patients were thrombocytopenia (8.9%) and neutropenia (6.7%).

Tabulated list of ADRs from clinical trials

The ADRs are listed below by MedDRA system organ class (SOC) and categories of frequency. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4 Summary of adverse drug reactions occurring in previously treated DLBCL patients treated with Polivy in combination with BR

Adverse drug reactions	Polivy + bendamustine + rituximab N = 45	Bendamustine + rituximab N=39
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SOC	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Infections and Infestations				
Pneumonia ^a	15.6	6.7	10.3	0
Blood and Lymphatic System Disorders				
Anemia	46.7	24.4	25.6	17.9
Neutropenia	46.7	40.0	38.5	33.3
Thrombocytopenia	46.7	37.8	28.2	23.1
Febrile Neutropenia	11.1	11.1	12.8	12.8
Leukopenia	11.1	6.7	12.8	7.7
Lymphopenia	11.1	11.1	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	26.7	2.2	20.5	0
Hypokalemia	15.6	6.7	7.7	2.6
Hypoalbuminemia	13.3	2.2	5.1	0
Hypocalcemia	11.1	2.2	2.6	0
Nervous System Disorders				
Neuropathy Peripheral	20.0	0	2.6	0
Dizziness	13.3	0	7.7	0
Peripheral Sensory neuropathy	13.3	0	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	15.6	0	20.5	0

Gastrointestinal Disorders				
Diarrhea	37.8	4.4	28.2	5.1
Nausea	33.3	0	41.0	0
Constipation	17.8	0	20.5	2.6
Vomiting	17.8	2.2	12.8	0
Abdominal Pain	11.1	4.4	10.3	2.6
Abdominal Pain Upper	11.1	2.2	5.1	0
Skin and Subcutaneous Tissue Disorders				
Pruritis	13.3	0	10.3	2.6
General Disorders and Administration Site Conditions				
Fatigue	40.0	4.4	35.9	2.6
Pyrexia	33.3	2.2	23.1	0
Asthenia	11.1	0	15.4	0
Chills	11.1	0	7.7	0
Investigations				
Weight decreased	15.6	2.2	7.7	2.6
Injury, Poisoning, and Procedural				
Infusion-related reaction ^b	33.3	6.7	23.1	10.3

^aADR associated with fatal outcome

^bDefined as all adverse events reported as related to study treatment within 24 hours after treatment infusion

Description of selected adverse drug reactions from clinical trials

In the Polivy plus BR arm, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia were reported in 40%, 37.8%, and 24.4% of patients, respectively.

Myelosuppression

8.9% of patients in the Polivy plus BR arm discontinued Polivy due to neutropenia compared to 2.6% of patients in the BR arm who discontinued treatment due to neutropenia. Thrombocytopenia events led to discontinuation of treatment in 11.1% of patients in the Polivy plus BR arm and 5.1% of patients in the BR arm. No patients discontinued treatment due to anemia in either the Polivy plus BR arm or BR arm.

Peripheral Neuropathy (PN)

In the Polivy plus BR arm, Grade 1 and 2 PN events were reported in 26.7% and 13.3% of patients, respectively. In the BR arm, Grade 1 and 2 PN events were reported in 2.6% and 5.1% of patients, respectively. No Grade 3-5 PN events were reported in either the Polivy plus BR arm or BR arm. 2.2% of patients discontinued Polivy treatment due to PN and 4.4% of patients had Polivy dose reduction due to PN. No patients in the BR arm discontinued treatment or had dose reductions due to PN. In the Polivy plus BR arm, the median onset to first event of PN was 1.8 months, and 61.1% of patients with PN events reported event resolution.

Infections

Infections, including pneumonia and other types of infections, were reported in 53.3% of patients in the Polivy plus BR arm and 51.3% of patients in the BR arm. In the Polivy plus BR arm, serious infections were reported in 28.9% of patients and fatal infections were reported in 8.9% of patients. In the BR arm, serious infections were reported in 30.8% of patients and fatal infections were reported in 10.3% of patients. One patient (2.2%) in the Polivy plus BR arm discontinued treatment due to infection compared to 5.1% of patients in the BR arm.

Progressive Multifocal Leukoencephalopathy (PML)

One case of PML, which was fatal, occurred in one patient treated with Polivy plus bendamustine and obinutuzumab. This patient had three prior lines of therapy that included anti-CD20 antibodies.

Hepatic toxicity

In another study, two cases of serious hepatic toxicity (hepatocellular injury and hepatic steatosis) were reported and were reversible.

Gastrointestinal Toxicity

Gastrointestinal toxicity events were reported in 80.0% of patients in the Polivy plus BR arm compared to 64.1% of patients in the BR arm. Most events were Grade 1-2, and Grade 3-4 events were reported in 22.2% of patients in the Polivy plus BR arm compared to 12.8% of patients in the BR arm. The most common gastrointestinal toxicity events were diarrhea and nausea.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no experience with overdose in human clinical trials. The highest dose tested to date is 2.4 mg/kg administered as an intravenous infusion; it was associated with a higher frequency and severity of PN events. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

5. PHARMACOLOGICAL PROPERTIES AND EFFECTS

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic agents; other antineoplastic agents; monoclonal antibodies

ATC code: L01XC37

Mechanism of action

Polatuzumab vedotin is a CD79b-targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B-cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanized immunoglobulin G1 (IgG1) monoclonal antibody via a cleavable linker. The monoclonal antibody binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor. CD79b expression is restricted to normal cells within the B-cell lineage (with the exception of plasma cells) and malignant B-cells; it is expressed in > 95% of DLBCL. Upon binding CD79b, polatuzumab vedotin is rapidly internalized and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.

Pharmacodynamic effects

Cardiac electrophysiology

Polatuzumab vedotin did not prolong the mean QTc interval to any clinically relevant extent based on ECG data from two open-label studies in patients with previously treated B-cell malignancies at the recommended dosage.

Clinical efficacy and safety

The efficacy of Polivy was evaluated in an international, multicenter, open-label study (GO29365) which included a randomized cohort of 80 patients with previously treated DLBCL. Patients were randomized 1:1 to receive Polivy plus BR or BR alone for six 21-day cycles. Patients were stratified by duration of response to last prior treatment of ≤ 12 months or > 12 months.

Eligible patients were not candidates for autologous hematopoietic stem cell transplant (HSCT) and had relapsed or refractory disease after receiving at least one prior systemic chemotherapy regimen. The study excluded patients with prior allogeneic HSCT, central nervous system lymphoma, transformed follicular lymphoma (FL), and grade 3b FL, significant cardiovascular or pulmonary disease, active infections, AST or alanine transaminase (ALT) $> 2.5 \times$ ULN or total bilirubin $\geq 1.5 \times$ ULN, creatinine $> 1.5 \times$ ULN (or CrCl < 40 mL/min) unless due to underlying lymphoma.

Polivy was given intravenously at 1.8 mg/kg administered on Day 2 of Cycle 1 and on Day 1 of Cycles 2-6. Bendamustine was administered at 90 mg/m² intravenously daily on Days 2 and 3 of Cycle 1 and on Days 1 and 2 of Cycles 2-6. Rituximab was administered at 375 mg/m² intravenously on Day 1 of Cycles 1-6.

Among the 80 patients who were randomized to receive Polivy plus BR (n=40) or BR alone (n = 40) the majority were white (71%) and male (66%). The median age was 69 years (range 30 to 86 years). Sixty-four out of 80 patients (80%) had ECOG performance score (PS) of 0-1 and 14 out of 80 patients (18%) had ECOG PS of 2. The majority of patients (98%) had DLBCL not otherwise specified (NOS). Overall, 48% of patients had activated B-cell (ABC) DLBCL and 40% of patients had germinal center B-cell like (GCB) DLBCL. Primary reasons patients were not candidates for HSCT included age (40%), insufficient response to salvage therapy (26%) and prior transplant failure (20%). The median number of prior therapies was 2 (range: 1-7) with 29% (n=23) receiving one prior therapy, 25% (n=20) receiving 2 prior therapies, and 46% (n=37) receiving 3 or more prior therapies. All except one patient in the pola+BR arm of the randomized Phase II were naïve to bendamustine treatment. 80% of patients had refractory disease.

The primary endpoint of the study was complete response (CR) rate at end of treatment (6-8 weeks after day 1 of cycle 6 or last study treatment) as assessed by independent review committee (IRC). Efficacy results are summarized in Table 5 and in Figures 1-3.

Table 5 **Summary of efficacy in patients with previously treated DLBCL from study GO29365**

	Polivy + bendamustine + rituximab N= 40	Bendamustine + rituximab N= 40
	Median observation time 22 months	
<i>Primary Endpoint</i>		
Complete Response Rate* (IRC-assessed) at End of treatment**		
Responders (%)	16 (40.0)	7 (17.5)
Difference in response rate (%) [95% CI]	22.5 [2.6, 40.2]	
p-value (CMH chi-squared test***)	0.0261	
<i>Key secondary and exploratory endpoints</i>		
Overall Survival		
Number (%) of patients with event	23 (57.5)	28 (70.0)
Median OS (95% CI), months	12.4 (9.0, NE)	4.7 (3.7, 8.3)
HR [95% CI]	0.42 [0.24, 0.75]	
p-value (Log-Rank test, stratified***)	0.0023 [¶]	
Progression Free survival (INV-assessed)		
Number (%) of patients with event	27 (67.5)	35 (87.5)
Median PFS (95% CI), months	7.6 (6.0, 17.0)	2.0 (1.5, 3.7)
HR [95% CI]	0.34 [0.20, 0.57]	
p-value (Log-Rank test, stratified***)	<0.0001	
Duration of response (INV-assessed)		
Number of patients included in analysis	28	13
Number (%) of patients with event	17 (60.7)	11 (84.6)
Median DOR (95% CI), months	10.3 (5.6, NE)	4.1 (2.6, 12.7)
HR [95% CI]	0.44 [0.20, 0.95]	
p-value (Log-Rank test, stratified***)	0.0321	

	Polivy + bendamustine + rituximab N= 40	Bendamustine + rituximab N= 40
	Median observation time 22 months	
Overall Response Rate* (INV-assessed) at End of Treatment**		
Responders (%) (CR, PR)	19 (47.5)	7 (17.5)
Difference in response rate (%) [95% CI]	30.0 [9.5, 47.4]	
p-value (CMH chi-squared test***)	0.0036	
Complete Response (%) (CR)	17 (42.5)	6 (15.0)
Difference in response rate (%) [95% CI]	27.5 [7.7, 44.7]	
p-value (CMH chi-squared test***)	0.0061	
Partial Response (%) (PR)	2 (5.0)	1 (2.5)
95% CI Clopper-Pearson	[0.6, 16.9]	[0.06, 13.2]
Best Overall Response Rate* (INV-assessed)		
Responders (%) [CR, PR]	28 (70.0)	13 (32.5)
Difference in response rate (%) [95% CI]	37.5 [15.6, 54.7]	
Complete Response (%) [CR]	23 (57.5)	8 (20.0)
95% CI Clopper-Pearson	[40.9, 73.0]	[9.1, 35.7]
Partial Response (%) [PR]	5 (12.5)	5 (12.5%)
95% CI Clopper-Pearson	[4.2, 26.8]	[4.2, 26.8]

IRC: Independent Review Committee; INV: Investigator; CI: Confidence Interval, HR: Hazard Ratio; CMH Cochran-Mantel-Haenszel; OS: Overall survival; NE: Not evaluable; PFS: progression free survival; DOR: Duration of response

*Per modified Lugano 2014 criteria: Bone marrow confirmation of PET-CT CR required. PET-CT PR required meeting both PET-CT criteria and CT criteria.

**6-8 weeks after day 1 of cycle 6 or last study treatment

*** Stratification by duration of response to prior therapy (≤ 12 months vs > 12 months)

Overall survival (OS) was an exploratory endpoint which was not type 1 error controlled. The median OS in the Polivy+BR arm was 12.4 months (95% CI: 9.0, NE) vs 4.7 months (95% CI: 3.7, 8.3) in the control arm. The unadjusted estimate for OS HR was 0.42. When accounting for the influence of baseline covariates the OS HR was adjusted to 0.59. Covariates included primary refractory status, number of prior lines of therapy, IPI, and prior stem cell transplant.

Investigator-assessed progression free survival (PFS) was an exploratory endpoint which was not type 1 error controlled. The median PFS in the Polivy+BR arm was 7.6 months (95% CI: 6.0,

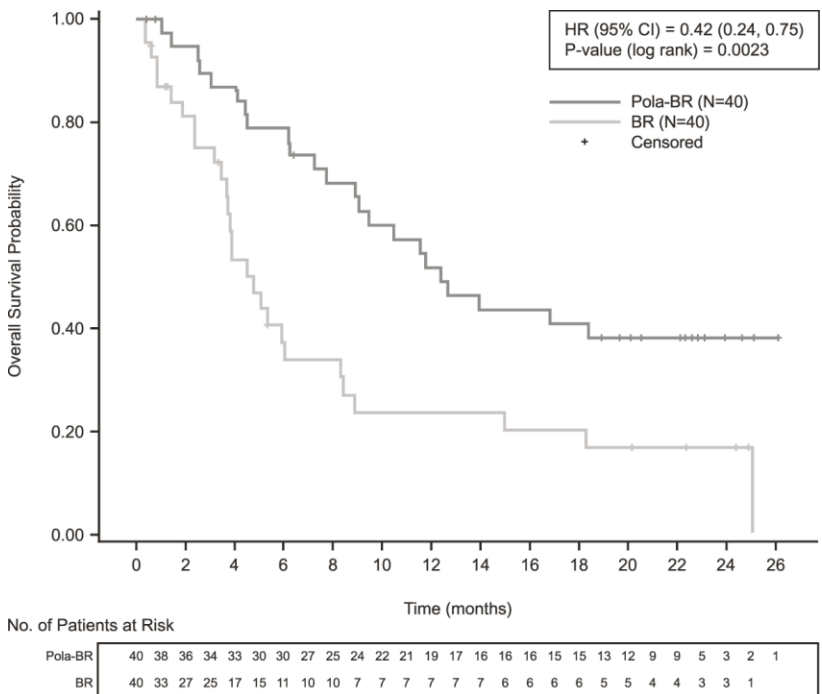
17.0) vs 2.0 months (95% CI: 1.5, 3.7) in the control arm. The unadjusted estimate for PFS HR was 0.34.

Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with polatuzumab vedotin. Across all arms of study GO29365, 8 out of 134 (6.0%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Across seven clinical studies, 14 out of 536 (2.6%) patients tested positive for anti-polatuzumab vedotin antibodies at one or more post-baseline time points. Due to the limited number of anti-polatuzumab vedotin antibody positive patients, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety.

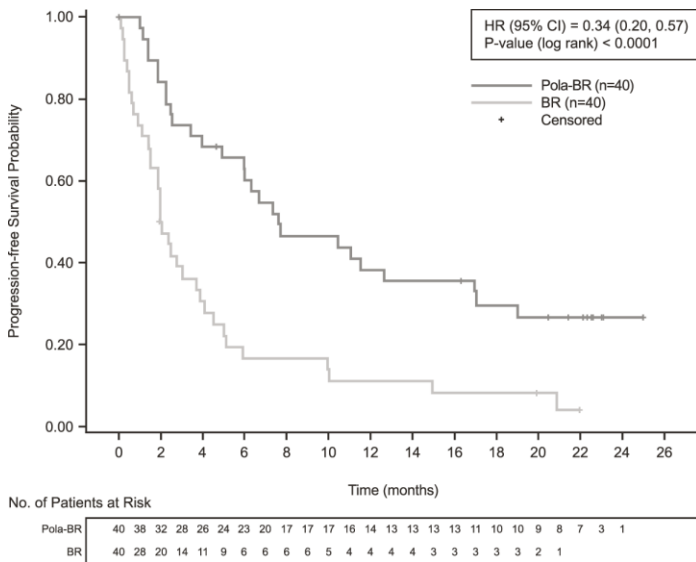
Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to polatuzumab vedotin with the incidence of antibodies to other products may be misleading.

Figure 1 Kaplan Meier curve of overall survival



No.: number; Pola: Polivy; BR: bendamustine and rituximab; HR: hazard ratio.

Figure 2 Kaplan-Meier curve of INV assessed progression-free survival

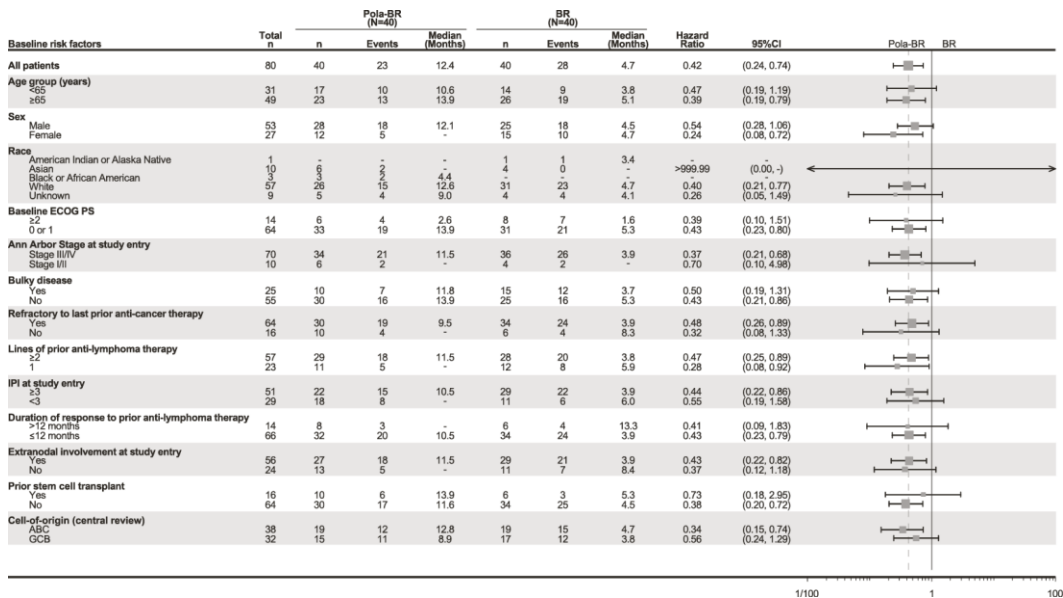


No.; number; Pola: Polivy; BR: bendamustine and rituximab; HR: hazard ratio.

Results of subgroup analyses

Results of subgroup analysis of overall survival were consistent with the results seen in the overall DLBCL population (see Figure 3 below).

Figure 3 Forest plot of Overall survival



ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPI: International Prognostic Index; ABC: activated B-cell; GCB: germinal center B-cell like; Pola: Polivy; BR: bendamustine and rituximab; CI: confidence interval

5.2 Pharmacokinetic Properties

Antibody-conjugated MMAE (acMMAE) plasma exposure increased dose-proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. After the first 1.8 mg/kg polatuzumab vedotin dose, the acMMAE mean maximum concentration (C_{max}) was 803 (\pm 233) ng/mL and the area under the concentration-time curve from time zero to infinity (AUC_{inf}) was 1860 (\pm 966) day*ng/mL. Based on the population PK analysis, Cycle 3 acMMAE AUC increased by approximately 30% over cycle 1 AUC, and achieved more than 90% of the Cycle 6 AUC. The terminal half-life at cycle 6 was approximately 12 days (95% CI of 8.1-19.5 days) for acMMAE. Based on population PK analysis, the predicted acMMAE concentration at the end of cycle 6 is approximately 80% of the theoretical steadystate value. Exposures of unconjugated MMAE, the cytotoxic component of polatuzumab vedotin, increased dose proportionally over the 0.1 to 2.4 mg/kg polatuzumab vedotin dose range. MMAE plasma concentrations followed formation rate limited kinetics. After the first 1.8 mg/kg polatuzumab vedotin dose, the C_{max} was 6.82 (\pm 4.73) ng/mL, the time to maximum plasma concentration is approximately 2.5 days, and the terminal half-life is approximately 4 days. Plasma exposures of unconjugated MMAE are < 3% of acMMAE exposures. Based on the population PK analysis there is a decrease of plasma unconjugated MMAE exposure (AUC) after repeated every-three-week dosing.

Based on population pharmacokinetics simulations, a sensitivity analysis predicted exposure to unconjugated MMAE for patients with bodyweight over 100 kg to be increased by 27%.

Absorption

Polivy is administered as an IV infusion. There have been no studies performed with other routes of administration.

Distribution

The population estimate of central volume of distribution for acMMAE was 3.15 L, which approximated plasma volume. *In vitro*, MMAE is moderately bound (71% - 77%) to human plasma proteins. MMAE does not significantly partition into human red blood cells *in vitro*; the blood to plasma ratio is 0.79 to 0.98.

In vitro data indicate that MMAE is a P-gp substrate but does not inhibit P-gp at clinically relevant concentrations.

Biotransformation

Polatuzumab vedotin is expected undergo catabolism in patients, resulting in the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE related catabolites. The levels of MMAE metabolites have not been measured in human plasma.

In vitro studies indicate that MMAE is a substrate for CYP 3A4/5 but does not induce major CYP enzymes. MMAE is a weak time-dependent inhibitor of CYP3A4/5 but does not competitively inhibit CYP3A4/5 at clinically relevant concentrations.

MMAE does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Elimination

Based on a population pharmacokinetic analysis, the conjugate (acMMAE) is primarily eliminated by non-specific linear clearance pathway with a value of 0.9 L/day. *In vivo* studies in rats dosed with polatuzumab vedotin (radiolabel on MMAE) demonstrate that the majority of radioactivity is excreted in feces and the minority of radioactivity is excreted in urine.

Pediatric Population

No studies have been conducted to investigate the pharmacokinetics of Polivy in pediatric patients (<18 years old).

Elderly

Age did not have an effect on the pharmacokinetics of acMMAE and unconjugated MMAE based on a population PK analysis with patients aged 20-89 years. No significant difference was observed in the pharmacokinetics of acMMAE and unconjugated MMAE among patients <65 years of age (n=187) and patients ≥65 years of age (n=273).

Renal impairment

In patients with mild (CrCL 60-89 mL/min, n=161) or moderate (CrCL 30-59 mL/min, n=109) renal impairment, acMMAE and unconjugated MMAE exposures are similar to patients with normal renal function (CrCL ≥ 90 mL/min, n=185), based on a population pharmacokinetic analysis. There are insufficient data to assess the impact of severe renal impairment (CrCL 15-29 mL/min, n=3) on PK. No data are available in patients with end-stage renal disease and/or who are on dialysis.

Hepatic impairment

In patients with mild hepatic impairment [AST >1.0 - 2.5×ULN or ALT >1.0 - 2.5×ULN or total bilirubin >1.0 - 1.5×ULN, n=54], acMMAE exposures are similar whereas unconjugated MMAE AUC are 40% higher compared to patients with normal hepatic function (n=399), based on a population pharmacokinetic analysis.

There are insufficient data to assess the impact of moderate hepatic impairment (total bilirubin >1.5 - 3×ULN, n=2) on PK. No data are available in patients with severe hepatic impairment or liver transplantation.

5.3 Preclinical safety data

Systemic toxicity

In both rats and cynomolgus monkeys, the predominant systemic toxicities associated with administration of MMAE and polatuzumab vedotin included reversible bone marrow toxicity and associated peripheral blood cell effects.

Genotoxicity

No dedicated mutagenicity studies have been performed with Polivy. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

MMAE was a genotoxic in the rat bone marrow micronucleus study probably through an aneugenic mechanism. This mechanism is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent.

Carcinogenicity

No dedicated carcinogenicity studies have been performed with polatuzumab vedotin and/or MMAE.

Impairment of fertility

No dedicated fertility studies in animals have been performed with Polivy. However, results of the 4-week rat toxicity study indicate the potential for polatuzumab vedotin to impair male reproductive function and fertility. Testicular seminiferous tubule degeneration did not reverse following a 6-week treatment-free period and correlated with decreased testes weight and gross at recovery necropsy of small and/or soft testes in males given ≥ 2 mg/kg.

Reproductive toxicity

No dedicated teratogenicity studies in animals have been performed with Polivy. However, treatment of pregnant rats with MMAE at 0.2 mg/kg caused embryoletality and fetal malformations (including protruding tongue, malrotated limbs, gastroschisis, and agnathia). Systemic exposure (AUC) in rats at a dose of 0.2 mg/kg MMAE is approximately 50% of the AUC in patients who received the recommended dose of 1.8 mg/kg Polivy every 21-days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Succinic Acid, Sodium Hydroxide, Sucrose, Polysorbate 20

6.2 Incompatibilities

- Do not mix Polivy with, or administer through the same infusion line, as other medicinal products.
- No incompatibilities have been observed between Polivy and IV infusion bags with product contacting materials of polyvinyl chloride (PVC), or polyolefins (PO) such as polyethylene (PE) and polypropylene (PP). In addition, no incompatibilities have been observed with infusion sets or infusion aids with product contacting materials of PVC, PE, polyurethane (PU), polybutadiene (PBD), acrylonitrile butadiene styrene (ABS),

polycarbonate (PC), polyetherurethane (PEU), or fluorinated ethylene propylene (FEP) and with filter membranes composed of polyether sulfone (PES) or polysulfone (PSU).

6.3 Shelf life

Unopened vial: 2 years

6.4 Special precautions for storage

Vials: Store unopened vials at 2°C to 8°C.

Keep vial in the outer carton in order to protect from light.

Do not freeze. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

The reconstituted solution and solution for infusion should not be frozen or exposed to direct sunlight.

6.5 Nature and contents of container

Single-dose vial 140 mg

6.6 Special Instructions for Use, Handling and Disposal

Polivy must be reconstituted using sterile water for injection and diluted into an IV infusion bag containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose by a healthcare professional prior to administration.

Use aseptic technique for reconstitution and dilution of Polivy. Appropriate procedures for the preparation of antineoplastic products should be used.

The reconstituted product contains no preservative and is intended for single-dose usage only. Discard any unused portion.

A dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 µm pore size) and catheter must be used to administer diluted Polivy.

Reconstitution

1. Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection into the 140 mg Polivy vial to yield a single-dose solution containing 20 mg/mL polatuzumab vedotin. Direct the stream toward the wall of the vial and not directly on the lyophilized cake.
2. Swirl the vial gently until completely dissolved. *Do not shake*
3. Inspect the reconstituted solution for discoloration and particulate matter. The reconstituted solution should appear colorless to slightly brown, clear to slightly opalescent, and free of visible particulates. Do not use if the reconstituted solution is discolored, cloudy, or contains visible particulates.

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 72 hours at 2°C to 8°C and up to 24 hours at room temperature (9°C to 25°C).

Dilution

1. Polatuzumab vedotin must be diluted to a final concentration of 0.72 – 2.7 mg/mL in an IV infusion bag with a minimum volume of 50mL containing 0.9% sodium chloride, 0.45% sodium chloride, or 5% dextrose.
2. Determine the volume of 20 mg/mL reconstituted solution needed based on the required dose:

$$\text{Volume} = \frac{\text{Polivy dose (1.8 or 1.4 mg/kg) X patient's weight (kg)}}{\text{Reconstituted vial concentration (20 mg/mL)}}$$

3. Using a sterile syringe, withdraw and discard a volume of diluent equivalent to the required volume of reconstituted solution from the IV infusion bag.
4. Withdraw the required volume of reconstituted solution from the Polivy vial using a sterile syringe and dilute into the IV infusion bag. Discard any unused portion left in the vial.
5. Gently mix the IV bag by slowly inverting the bag. *Do not shake.*
6. Inspect the IV bag for particulates and discard if present.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Acceptable chemical and physical stability of the prepared solution for infusion has been demonstrated for the durations listed in Table 6. Discard if storage time exceeds these limits. *Do not freeze or expose to direct sunlight.*

Table 6 Durations for which acceptable chemical and physical stability of the prepared solution for infusion have been demonstrated

Diluent used to prepare solution for infusion	Solution for infusion storage conditions ¹
0.9% Sodium Chloride	Up to 24 hours at 2°C to 8°C or up to 4 hours at room temperature (9°C to 25°C)
0.45% Sodium Chloride	Up to 72 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)
5% Dextrose	Up to 72 hours at 2°C to 8°C or up to 8 hours at room temperature (9°C to 25°C)

¹To ensure product stability, do not exceed specified storage durations.

Avoid transportation of the prepared solution for infusion as agitation stress can result in aggregation. If the prepared solution for infusion will be transported, remove air from the infusion bag and limit transportation to 30 minutes at 9°C to 25°C or 2 hours at 2°C to 8°C. If air is removed, an infusion set with a vented spike is required to ensure accurate dosing during the infusion.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

Made for F. Hoffmann-La Roche Ltd., Basel, Switzerland by

BSP Pharmaceuticals S.p.A., Italy

Imported by Roche Thailand Ltd., Bangkok

8. Marketing Authorization Numbers

Reg.No. 1C XXXXXXX/63 (NBC)

9. Date of authorization

XXXXXXXXXX

10. Date of revision of the text

Current at December 2018

Medicine: keep out of reach of children
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